REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims under examination be allowed.

Claim Amendments

Claims 52-56 have been canceled without prejudice or disclaimer.

Claims 5-8, 11, 12, 21-23, 27-29, 32-34, 38-40, 49-51, 43-45 and 60-62 have been amended to recite "host cell" instead of "transformant". Support for this recitation can be found, for example, at page 4, lines 19-22.

Claims 23, 25, 30, and 47 have been rephrased for additional clarity.

Claim 41 has been amended to delete the phrase "or a fragment thereof".

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicants submit that all claim amendments presented herein or previously are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability. Applicants reserve the right to file at least one continuing application to pursue any subject matter that is canceled or removed from prosecution due to the amendments.

Rejections Under 35 U.S.C. §102 and 35 U.S.C. §103

Claims 1-8, 11, 12 and 18-62 stand rejected under 35 U.S.C. §102(b) or alternatively under 35 U.S.C. §103(a) in view of Gmerek *et al.* (Genbank Accession No. U13395). Claims 52-56 have been canceled. Applicants respectfully traverse the rejections with respect to claims 1-8, 11, 12, 18-51 and 57-62, as amended.

35 U.S.C. §102

The standard of anticipation under 35 U.S.C. §102 is that each and every element of the claim must be found in the cited reference. *In re Marshall*, 198 USPQ 344 (CCPA 1978).

The claimed invention relates to isolated nucleic acids encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2, fragments or variants thereof, host cells harboring the sequences, and their uses. Gmerek *et al.* teach the HHCMA56 cDNA sequence, which is 98.6% identical to a fragment (nucleotides 578-2052) of SEQ ID NO:1. Compared to nucleotides 578-2052 of SEQ ID NO:1, the HHCMA56 cDNA sequence contains two additional nucleotides in the coding region, and thus would be translated out of frame from nucleotide 275 on. However, the Office Action deems the cDNA cloned by Gmerek *et al.* ("the Gmerek molecule") to be inherently the same as the cDNA disclosed in the present application. Accordingly, the Office Action takes the position that Gmerek *et al.* inherently anticipate the claimed invention.

Regardless of whether the Gmerek molecule is inherently the same as part of SEQ ID NO:1 (and Applicants reserve the right to contest this notion), it is clear that the Gmerek molecule cannot be the same as more than a portion (nucleotides 578-2052 of SEQ ID NO:1) of the cDNA of the present application. Thus, Gmerek *et al.* cannot possibly anticipate any of the presently pending claims, for the reasons set forth below.

Nucleotides 578 to 2052 of SEQ ID NO:1 encode amino acids 152-414 of SEQ ID NO:2[1]. Claim 1 is drawn to a nucleic acid that encodes a polypeptide containing the entire SEQ ID NO:2. Gmerek *et al.* disclose, at most, a fragment of the claimed nucleic acid. There is no basis for assuming that the Gmerek molecule contained any more sequence than what was reported in Gmerek *et al.* Therefore, the reference does not anticipate this claim.

[1] In fact, since the first ATG in the Gmerek molecule starts at nucleotide 19 of that sequence, the Gmerek molecule would inherently encode, at most, only amino acids 158-414 of SEQ ID NO:2 (provided that the Examiner is correct in saying that the two extra nucleotides at positions 276 and 280 of the sequence disclosed in Gmerek et al. were sequencing errors and in fact were not inherently present in the Gmerek molecule itself).

Claim 2 requires a nucleic acid that encodes the entire SEQ ID NO:2, or a fragment thereof that has a function associated with maintenance of differentiation of smooth muscle cells equivalent to that of the protein consisting of SEQ ID NO:2 ("the smooth muscle function"). Even if the Gmerek molecule could be said to inherently encode residues 152-414 of SEQ ID NO:2, it lacks the two WW domains that are presumably important for the smooth muscle function. As disclosed in the present application, the protein consisting of SEQ ID NO:2 contains two WW domains in the N-terminal region that participate in protein-protein interaction (page 5, lines 5-7). This suggests that the protein binds to other proteins and regulates intracellular signal transduction, gene expression or the like, and thereby participates in the maintenance of differentiation of smooth muscle cells (page 5, lines 7-9). The WW domains are not found in the HHCMA56 sequence (page 41, line 8). The WW domains were identified by analyzing SEQ ID NO:2 using the pfam motif database (page 2, lines 22-25). A copy of this analysis is attached hereto as Exhibit A, which shows that the WW domains are located at amino acids 18-47 and 59-88, respectively. Clearly, the Gmerek molecule, which at most inherently encodes residues 152-414 of SEQ ID NO:2, does not contain the WW domains.

Since the protein encoded by the Gmerek molecule does not contain the WW domains, it presumably does not have the smooth muscle function required by the claim. To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference. Inherency, however, may not be established by probabilities or possibilities. *In re Robertson*, 49 USPQ2d 1949, 1950-1951 (Fed. Cir. 1999). MPEP §2112. Here, it appears highly unlikely that the Gmerek molecule encodes a protein that possesses the smooth muscle function. Since the Gmerek molecule does not meet the "necessarily" standard of inherency, claim 2 is not inherently anticipated.

Claim 19 requires the entire coding sequence of SEQ ID NO:1, so it is not inherently anticipated by the Gmerek molecule.

Claim 24 requires that the encoded polypeptide comprise the entire SEQ ID NO:2 except for up to 10 amino acid substitutions, deletions or insertions. The Gmerek molecule lacks the sequence encoding residues 1-151 of SEQ ID NO:2. Therefore, it differs from SEQ ID NO:2 by more

than 10 amino acids and does not inherently anticipate claim 24. In addition, claim 24 requires that the encoded polypeptide exhibit the smooth muscle function. As discussed above, the polypeptide inherently encoded by the Gmerek molecule may very well not have this function, so it does not meet the "necessarily" standard for inherent anticipation.

Similarly, claim 30 is not inherently anticipated by Gmerek *et al.* because the claim requires the smooth muscle function, and the polypeptide inherently encoded by the Gmerek molecule probably does not have the smooth muscle function.

Claim 35 requires that the encoded amino acid sequence be at least 95% identical to SEQ ID NO:2. A polypeptide consisting of residues 152-414 of SEQ ID NO:2 has only 64% sequence identity with SEQ ID NO:2. Furthermore, this claim requires the smooth muscle function. Thus, claim 35 is not inherently anticipated.

Claim 41, as amended, requires that the encoded polypeptide comprise the entire SEQ ID NO:2. Again, it is not inherently anticipated by the reference, which at most discloses part of SEQ ID NO:2.

Claim 46 limits the encoded polypeptide to one that is no more than 10 amino acids different from SEQ ID NO:2, and claim 57 requires an encoded amino acid sequence at least 95% identical with SEQ ID NO:2, neither of which encompasses the Gmerek molecule.

In sum, the reference does not disclose each and every element of any of the claims discussed above. All the other rejected claims depend from one of the claims discussed above, and hence are also not anticipated by the reference.

Accordingly, withdrawal of this rejection is respectfully requested.

35 U.S.C. §103

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a prima facie case of obviousness by meeting three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally

available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). Second, there must be a reasonable expectation of success. Id. Finally, the prior art reference or the combination of references must teach or suggest all the claim limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974).

These criteria are not met by the present rejection. As discussed above, the claimed invention relates to nucleic acids that are highly similar to SEQ ID NO:1 or those that encode a polypeptide having the smooth muscle function. Even if what the Examiner characterizes as sequencing errors in Gmerek *et al.* were corrected, and even if the coding sequence of Gmerek *et al.* were deemed to begin at residue 1 instead of at the first ATG (codon residues 19-21), Gmerek *et al.* would, at most, inherently disclose a fragment of SEQ ID NO:1 that contains only 64% of the coding sequence of SEQ ID NO:1 and that encodes a polypeptide unlikely to possess the smooth muscle function required by some of the claims. There is no motivation or suggestion in Gmerek *et al.* to modify their teaching to arrive at the claimed invention. The reference also does not offer any reasonable expectation of success for, or disclose all the elements of, the claimed invention. Therefore, the criteria for a *prima facie* case of obviousness have not been met.

Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

Claims 5-8, 11-13, 20-23, 27-29, 32-34, 38-40, 43-45, 49-51, 54-56 and 60-62 stand rejected under 35 U.S.C. §101, as allegedly lacking patentable utility. The Office Action states that these claims are drawn to transformants, and as such read on transgenic animals that allegedly lack patentable utility. The Office Action further rejects these claims under 35 U.S.C. §112, first paragraph, on the ground that the transgenic animals are allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants disagree, because the present application provides sufficient disclosure to satisfy the utility and written description requirements for the transgenic animals at issue. However, in the sole interest of expediting allowance of the present application, claims 54-56 have been canceled. Each of the other rejected claims, as amended, is now drawn to a host cell. As a result, the claims do not read on transgenic animals, and the rejections are moot.

Accordingly, Applicants respectfully request that these rejections be withdrawn.

Conclusions

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's and rejections are hereby requested. Allowance of the claims remaining in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (617) 542-5070 or the undersigned's associate, Ping Hwung, at (650) 839-5044.

Enclosed is a $110.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: October 4, 2004

Reg. No. 44,164

For Janis K. Fraser, Ph.D., J.D.
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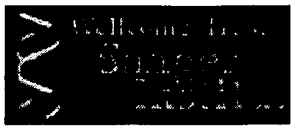
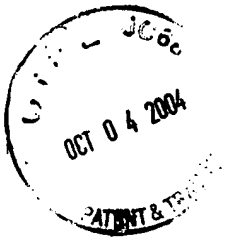
Protein families database of alignments and HMMs



Results for Userseq

EXHIBIT A



Retrieve result for id: 119g39XA96dY02DHX4 retrieve

HMMPFAM results are kept on our servers for two weeks following query submission. Results may be retrieved any number of times during this period. After this time queries must be resubmitted if further examination is required.

Trusted matches - domains scoring higher than the gathering threshold

Domain	Start	End	Bits	Evalue	Alignment	Mode
WW	18	47	45.10	1.3e-10	Align	ls
WW	59	88	45.80	8.4e-11	Align	ls
adh_short	127	383	59.30	7.2e-15	Align	ls

Matches to Pfam-B

Domain	Start	End	Alignment
Pfam-B_73450	177	232	Align
Pfam-B_1143	290	334	Align
Pfam-B_553	353	414	Align


[414 residues] Save image

WW 18-47

WW 59-88

adh_short 127-383

Potential matches - Domains with Evalues above the cutoff

Domain	Start	End	Bits	Evalue	Alignment	Mode
Pep_deformylase	73	85	3.20	0.65	Align	fs

Alignments of Pfam-A domains to HMMs

Format for fetching alignments to seed [Hypertext linked to swisspfam]

▶ Alignment of WW vs UNKNOWN-QUERY/18-47

```
                *->lppgWeerkdpdGrpYYyNhnTktTqWekP<-*
                   lppgWeer++ dG +YY Nh    +TqWe+P
UNKNOWN-QU    18   LPPGWEERTTKDGWVYYANHTEEKTQWEHP    47
```

Align to seed

▶ Alignment of WW vs UNKNOWN-QUERY/59-88

```
                *->lppgWeerkdpdGrpYYyNhnTktTqWekP<-*
                   lp gWe+ +d++G++++++h++k+T++ +P
UNKNOWN-QU    59   LPYGWEQETDENGQVFFVDHINKRTTYLDP    88
```

Align to seed

▶ Alignment of adh_short vs UNKNOWN-QUERY/127-383

```
                *->aLVTGassGIGlaiAkrLakeGakVvvvdrreekaeqaaaelkaelG
                   ++VTGa sGIG+++Ak +a  Ga+V++++r+ ++a +a+  + +e
UNKNOWN-QU   127   VVVTGANSGIGFETAKSFALHGAHVILACRNMARASEAVSRILEEWH 173

                .dralfiqlDvtdeeevkaavataverlGdrlDvLVNNAGilgdgppfee
                ++++++ +lD++   +v+ ++++ +++   +l+vLV+NA       p
UNKNOWN-QU   174 kAKVEAMTLDLALLRSVQHFAEAFKAKNV-PLHVLVCNAATFA--LPWS- 219

                lseedwervidvNltGvfllravlpamdhmlkrkgGrIVNisSvaGlr.
                l+++  e +++vN  G f l++++ +    + +    r++++sS + + +
UNKNOWN-QU   220 LTKDGLETTFQVNHLGHFYLVQLLQD---VLCRSAPARVIVVSSESHRFt 266

                ..................vgvpglsaYsASKaAvigltrsLAlElaphgG
                + +++ ++ + ++ ++++  + ++ aY  SK   i ++  L++ l p+g
UNKNOWN-QU   267 dindslgkldfsrlsptkNDYWAMLAYNRSKLCNILFSNELHRRLSPRG- 315

                IrVnavaPGgvdTdmtkalrsrligakkkarevkdiidpeleerllsrii
                ++ nav+PG +     +++++           v    +  +  +   +
UNKNOWN-QU   316 VTSNAVHPGNMMYSNIHRSWW----------V---YTLLFTLARPFTK- 350
```

```
                  plgrlgttpeeianavlfLasdaasysvtgqtltvdggi<-*
                   +++++      + +av  L   +  y ++     + +  +
UNKNOWN-QU    351 SMQQGA-ATTVYCAAVPELEGLGGMY-FN----NCCRCM     383
```

Align to seed

▶ Alignment of Pep_deformylase vs UNKNOWN-QUERY/73-85

```
                  *->vLFyDRisplkpl<-*
                     v+F+D+i+++ +
UNKNOWN-QU     73    VFFVDHINKRTTY     85
```

Align to seed

Alignments of Pfam-B domains to best-matching to Pfam-B sequence

Format for fetching alignments to Pfam-B families: Hypertext linked to swisspfam

▶ Query UNKNOWN-QUERY/177-232 matching Pfam-B_73450

```
          temp 177 VEAMTLDLALLRSVQHFAEAFKAKNVPLHVLVCNAATFALPWSLTKDGLE 226
                   VEAMTLDLALLRSVQHFAEAFKAKNVPLHVLVCNAATFALPWSLTKDGLE
UNKNOWN-QUERY 177 VEAMTLDLALLRSVQHFAEAFKAKNVPLHVLVCNAATFALPWSLTKDGLE 226

          temp 227 TTFQVN 232
                   TTFQVN
UNKNOWN-QUERY 227 TTFQVN 232
```

Align to family

▶ Query UNKNOWN-QUERY/290-334 matching Pfam-B_1143

```
          temp 290 MLAYNRSKLCNILFSNELHRRLSPRGVTSNAVHPGNMMYSNIHRS 334
                   MLAYNRSKLCNILFSNELHRRLSPRGVTSNAVHPGNMMYSNIHRS
UNKNOWN-QUERY 290 MLAYNRSKLCNILFSNELHRRLSPRGVTSNAVHPGNMMYSNIHRS 334
```

Align to family

▶ Query UNKNOWN-QUERY/353-414 matching Pfam-B_553

```
          temp 353 QQGAATTVYCAAVPELEGLGGMYFNNCCRCMPSPEAQSEETARTLWALSE 402
                   QQGAATTVYCAAVPELEGLGGMYFNNCCRCMPSPEAQSEETARTLWALSE
UNKNOWN-QUERY 353 QQGAATTVYCAAVPELEGLGGMYFNNCCRCMPSPEAQSEETARTLWALSE 402
```

```
          temp 403 RLIQERLGSQSG 414
               RLIQERLGSQSG
UNKNOWN-QUERY 403 RLIQERLGSQSG 414
```

Align to family

Comments or questions on the site? Send a mail to **pfam@sanger.ac.uk**